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COMMENTARY

Clinical trials in molecular radiotherapy—Tribulations and Triumphs Report of the NCRI CTRad meeting held at the Lift Islington, 8 June 2018

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ABSTRACT

It has been almost a decade since the commentary *Molecular radiotherapy — the radionuclide raffle?* by Gaze and Flux (2010). The overarching feeling then was that no individual or organisation has taken up the challenge, nationally or internationally, of championing molecular targeted radionuclide therapy in all its aspects. Here, we report on the recent NCRI-CTRAd (Clinical Trials in Molecular Radiotherapy-Tribulations and Triumphs) meeting, held in London on the 8 June 2018. The meeting was organized by the NCRI-CTRAd to review the challenges and opportunities for clinical trials in molecular radiotherapy, particularly focussing on investigator-led trials that incorporate imaging and dosimetry, and to discuss how the community can move forward. This meeting was organised in conjunction with the British Nuclear Medicine Society and reflects the progress of Nuclear Medicine in the UK.

Today the situation is much reversed with radiotherapeutics growing into a market worth many 10's of billions.¹ Two agents have recently been approved by the FDA for clinical use, *i.e.* Radium-223 dichloride (Xofigo[®]—indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease) and Lutetium Lu-177 DOTATATE (LUTATHERA[®]—indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours—GEPNETs). In addition, there are several working groups in the UK [Internal Dosimetry Users Group—IDUG; Clinical and Translational Radiotherapy Research Working Group—CTRAd, British Nuclear Medicine Society (BNMS) molecular radiotherapy group] and internationally (Internal Dosimetry Task Force of the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging Medical Internal Radiation Dose Committee) advocating the utility of MRT.

Radioiodine therapies still form the backbone of the MRT services in the UK, with ²²³Ra, ⁹⁰Y-SIRT and peptide receptor radionuclide therapy (*e.g.* Lu-177 DOTATATE) now becoming routine services. As the

number and variety of MRT procedures advances alongside renewed calls for improved planning of these therapies, taking advantage of the increased quantitative accuracy of radioisotope imaging, the nuclear medicine community is facing a paradigm shift in the management of MRT. Improvement of the MRT service requires input from a multidisciplinary team. The National Cancer Research Institute (NCRI)'s CTRAd published a review of MRT research in the UK in 2016.² The report identifies three strategic priorities and provides a number of recommendations for each that will promote progress in MRT research. The report addresses the need to enhance research infrastructure and multidisciplinary working and for more multicentre MRT trials with a national QA programme to standardize methods between centres. It also pointed out that staff need more time to devote to building and providing a dosimetry service for individualized MRT treatment planning. Realizing the unfulfilled potential of MRT will require an integrated approach, increased investment and the active involvement of a range of individuals and organizations beyond the NHS.

Here, we report on the recent NCRI-CTRad (Clinical Trials in Molecular Radiotherapy—Tribulations and Triumphs) meeting, held in London on the 8 June 2018. The meeting was organized by the NCRI-CTRad to review the challenges and opportunities for clinical trials in MRT, particularly focussing on investigator-led trials that incorporate imaging and dosimetry, and to discuss how the community can move forward. This meeting was organized in conjunction with the BNMS and reflects the progress of Nuclear Medicine in the UK. Ultimately the aim was to connect individuals from disparate disciplines working in the field of MRT. By facilitating a platform to discuss research interests and by critically evaluating ongoing clinical trials in MRT it was hoped to initiate new multidisciplinary collaborative efforts to progress this field. This meeting further underscored the role of CTRad in aiding the development of research ideas into funded clinical studies.

PRESENTATIONS

The changing landscape of molecular radiotherapy Professor John Buscombe, Consultant Nuclear Medicine Physician at Cambridge University Hospitals and current president of the BNMS, opened the meeting by providing a historical overview of the role of Nuclear Medicine in the changing and challenging landscape of MRT. Nuclear Medicine became a mono-speciality in 1989, yet there still remains a large variation in Nuclear Medicine departments with few centres equipped to provide therapy beyond the use of ^{131}I in the treatment of differential thyroid cancer (DTC). The success of the NETTER-1 study³ was highlighted, yet in stark contrast and despite the use of peptide receptor radionuclide therapy over the past 20 years in many nuclear medicine centres in the UK, there is a lack of funding and support from national bodies such as the National Institute for Health and Clinical Excellence. Notwithstanding this lack of funding and investment, the use of theragnostic approaches (^{68}Ga -PSMA / ^{177}Lu -PSMA) in the treatment of metastatic castrate-resistant prostate cancer (mCRPC) is fast gaining ground, with the first-in-man treatment concept using the imaging-therapy pair ^{68}Ga -PSMA/ ^{213}Bi -PSMA, recently reported.⁴ There are a plethora of new MRT constructs entering clinical trials with heavy investment worldwide in MRT and MRT centres. To accelerate this global trend in the UK, specialists are required to support the drive for MRT and more robust clinical trials are needed which again emphasizes the need for funding.

Professor Joe O'Sullivan, Consultant Oncologist at Queens University, Belfast gave a presentation entitled *MRT for bone metastases from prostate cancer*. Approximately 90% of patients with CRPC have bone metastases, which is also the main cause of death in this patient group. The phenotype of prostate cancer in bone facilitates both imaging and therapy. Bone seeking radionuclides can be classified either as calcium analogues (^{89}Sr or ^{223}Ra) or attached to a phosphate (^{153}Sm EDTMP, ^{186}Re HEDP, ^{188}Re or ^{32}Ph). Clinical trials with single agent β -emitting radionuclides have been limited by haematological toxicity and although showing a 40–60% pain response rate after therapy, there has been no demonstrable survival benefit. On the other hand, the ALSYMPCA trial

with ^{223}Ra showed an increased overall survival benefit with little associated toxicity.^{5,6} To improve the therapeutic ratio of ^{223}Ra , the ERA-223 trial initiated in 2016 evaluated the use of Abiraterone in conjunction with ^{223}Ra . However, due to the large number of bone fractures seen with the combined treatment recruitment was stopped. This trial highlighted the need for timing of the combined therapy, which was taken on board in the design of the ADRRAD trial (Belfast) where Docetaxel is given prior to the ^{223}Ra cycles.⁷ At the time of writing, no unexpected or dose limiting toxicities have been observed in the 29/30 patients recruited. He concluded that a new era for bone targeting with MRTs has commenced, but that many questions regarding the value and safety of combination therapies, initiation of therapy in the CRPC disease course, the response assessment either using whole body MRI or PSMA PET detection and interaction between ^{223}Ra and the bone microenvironment, remain unanswered.

Dr Kim Orchard, Consultant Haematologist from Southampton, gave a detailed overview of their *Trial experience with anti-CD66 for myeloma*, outlining the role of radiotherapy in bone marrow transplantation. Traditionally, transplant conditioning schedules have involved the use of total body irradiation for disease eradication. However, this is associated with high toxicity and an alternative is the use of targeted radiotherapy with a radiolabelled anti-CD66 monoclonal antibody. Anti-CD66 is bound in the bone marrow and therefore provides a useful target for bone marrow conditioning. ^{111}In -labelled anti-CD66 is used for biodistribution and dosimetry determination. If dosimetry outcomes were favourable, treatment uses ^{90}Y as the therapeutic isotope. Dose escalation was performed to determine the maximum tolerated dose in a Phase 1 trial, prior to proceeding to Phase 2. For patients in Phase 2, up to 35 Gy was delivered to the bone marrow, and a linear relationship obtained between infused activity of ^{90}Y and the radiation dose delivered to the bone marrow.

Following the success of this treatment, the principle has now been extended to a paediatric trial in relapsed/refractory leukaemia, between Great Ormond Street Hospital and University College London Hospital. This is a dose escalating protocol prior to allogeneic haematopoietic stem cell transplantation, with activity levels of 35, 45, 50 and 55 MBq/Kg. The trial is currently underway with successful implementation at the lower activity levels.

Dosimetry and radiochemistry

Dr Matthew Aldridge, University College London Hospitals, highlighted the need for dosimetry in his talk entitled *Dosimetry for MRT*. The concept of theragnostics was introduced, emphasizing the principle of disease staging with imaging of a radiopharmaceutical, followed by therapy with the therapeutic version. However, despite this personalised approach, there is still an uncertain relationship between the administered activity (in GBq) and the absorbed radiation dose (in Gy) to both the tumour and the normal tissues, which, if evaluated, would render the treatment more personalized, with potentially improved outcomes. It was shown that whilst there is a

good correlation between tumour absorbed dose and response, there is in fact, a wide range of tumour absorbed doses for a given activity and the appropriate modulation of treatments would likely bring MRT into the realm of conventional radiotherapy with tumour control probability balanced against normal tissue damage. The methodology of performing MRT dosimetry was presented, as well as the resource implications—including extra imaging sessions—that are required. However, this initial investment must be balanced by the improved patient outcomes and associated financial benefits, including the reduced related disease complications of a successful treatment. In addition, resource intensive MRT treatments may be contraindicated if dosimetry indicates unfavourable tumour absorbed doses. MRT dosimetry is conceptually easy to perform, and satisfies NHS forward planning of biomarker driven, personalized treatments with demonstrable outcomes that will significantly aid the NHS deliverable of improving cancer survival rates.

Dr Joseline Tan, Head of Radiopharmacy at the Royal Marsden NHS Foundation Trust presented a talk entitled *Radiochemistry for MRT*. Dr Tan introduced the radiopharmacy's role in setting up clinical trials using radiopharmaceuticals and the challenges they need to overcome. The radiopharmacy plays a critical role in the acquisition, preparation, accountability and distribution of radiopharmaceuticals used in clinical research. Radiopharmacy-specific issues need to be considered for Clinical Trial Investigational Medicinal products. Therefore, they need to be involved at the early stages of the trial setup and in the sponsor's site feasibility assessment, as they will need to ensure they have the necessary staff, resources, processes, licenses and environment agency permits in place.

Dr Mark Gaze, Consultant Clinical Oncologist at University College London Hospitals and Great Ormond Street Hospital for Children, conferred the many tribulations and triumphs when conducting *Clinical trials for children and young people*. This is a challenging cohort of patients to treat, requiring a vast infrastructure associated with a multidisciplinary approach of treatment. The LUDO trial, a Phase 2 paediatric trial evaluating the use of ^{177}Lu -DOTATATE in a relapsed/refractory neuroblastoma, was presented. This trial demonstrated how dosimetry was used to modulate administered activities based on whole body absorbed doses. Tumour and organ at risk dosimetry was also assessed, and treatment was well tolerated in this heavily pre-treated cohort.

Whilst the triumph of using a novel treatment regimen within a clinical trial context was noted, the time scale of putting this trial into practice was regarded as a tribulation with 10 years taken to develop the concept, obtain ethics applications/approvals and then to conduct a trial with patient recruitment, data acquisition and data analysis. This is in keeping with regulatory requirements and clinical trial management but does negate the essential element of acquiring an evidence base as rapidly as possible. Given the time scales required to implement a clinical trial, it is prudent to commence conceptualising new treatment protocols in parallel with existing ones.

Whilst LUDO outcomes are being evaluated, a new option for relapsed/refractory neuroblastoma is available with the MiNiVan trial—a combination of ^{131}I -mIBG, nivolumab and Dinutuximab β antibodies, which is the first transatlantic trial for this disease.

A further trial—Veritas—to open across Europe will evaluate the role of ^{131}I -mIBG in neuroblastoma in a randomized trial with high-dose chemotherapy. In this trial, the role of MRT will also be implemented earlier in the treatment regime, after induction chemotherapy.

Clinical trials for differentiated thyroid cancer

Dr Kate Garcez, Consultant Clinical Oncologist at the Christie Hospital in Manchester and clinical lead for thyroid cancer, gave a presentation entitled *Challenges for radioiodine treatment of DTC*. Radioiodine has been administered for over 40 years to treat DTC. The administered activity depends on the patient's risk stratification. The prognosis for low risk patients, treated with low radioiodine activities to ablate thyroid remnants following surgery, is excellent. However, radioiodine may be overtreating some of these patients leading to the IoN and ESTIMABL 2 trials.^{8,9} The optimal activity to treat high risk patients is unclear. Empirical activities of 3.5–5.5 GBq are commonly used. The absorbed dose to lesions ranges from <1 to 100 Gy. There is a need to identify the threshold absorbed dose for successful treatment or to implement methods to administer as high as safely achievable activities in combination with lesion dosimetry to avoid under treatment of high-risk patients.^{10,11} However, dosimetry is challenging in clinical practice due to the need for extra scanning and resources. More trials are required to assess the efficacy of dosimetry in treatment management. Dr Garcez concluded her presentation by stating that “In an era of increasingly precise delivery of radiation there is a need to better understand likely absorbed dose, in order to optimise [radioiodine] use in metastatic and high-risk patients.”

Dr Jon Wadsley, Consultant Clinical Oncologist at Weston Park Hospital and the Clinical Lead for the North Trent Cancer Research Network, opened this session with a summary of the challenges in setting up the *SELIMETRY* trial.¹² The primary end point of this Phase 2 trial is to assess Selumetinib-enhanced radioiodine therapy in DTC patients that are refractory to radioiodine. Selumetinib is a MEK kinase inhibitor believed to allow re-expression of sodium iodide symporters and therefore allow the patient a further option of radioiodine treatment. The response to this therapy is likely to relate to the absorbed dose. This is the first multicentre trial to incorporate single-photon emission CT (SPECT/CT) based dosimetry and an exploratory endpoint is to assess the feasibility of this approach for treatment management. This is a relatively complex study, requiring the patient to have multiple^{3,4} quantitative ^{123}I and ^{131}I SPECT/CT scans that has been reflected in its expense.

The first network of centres capable of performing radioiodine SPECT/CT based dosimetry in a harmonized way is being set up

for the SELIMETRY trial. This network will ensure there is no bias in dosimetry results between centres.

Dr Rebecca Gregory, Principal Radioisotopes Physicist in the Joint Department of Physics at the Royal Marsden Hospital gave a presentation on *Multicentre setup for dosimetry trials* in the UK. Commercially available SPECT/CT systems are not currently set up to provide quantitative radioiodine imaging. Therefore SPECT/CT systems at each site were calibrated to convert the γ photon count rates to activities for use in dosimetry calculations. These count rates are not linear with activity for therapeutic activities (GBq) of ^{131}I , therefore the count rate response of each system must be characterized to correct for this non-linearity. In addition to this partial volume effects need to be corrected for small objects. Therefore, volume specific calibration factors have also been measured. A library of calibration factors has been established at RMH so that trial images can be quantified, and dosimetry performed centrally. This is currently necessary to ensure that dosimetry is performed in a reproducible way to avoid method-related bias in the dosimetry results. The imaging and dosimetry network built for this trial will facilitate further studies.

The NCRI Radiotherapy Trials Quality Assurance (RTTQA) Team provides QA programmes for radiotherapy treatment planning of all UK Clinical Research Network Portfolio trials. External beam radiotherapy (EBRT) clinical trials currently undergo rigorous QA to ensure the safety, consistency and accuracy of delivered treatment. Elizabeth Miles, Coordinator for the RTTQA team, gave a presentation, *RTTQA for MRT*, outlining the QA process and the challenges of introducing similar procedures to MRT research. The QA process for EBRT involves a facility questionnaire and guidelines for image target and organ at risk outlining, treatment planning and optimization, delivery and verification and dosimetry audit. Prior to data accrual, centres plan a benchmark case following the trial protocol and improve their adherence to the protocol on the RTTQA feedback. Dosimetry audits are used during accrual to ensure continued compliance. Centres are approved for planning specified anatomical sites for protocols used in multiple trials. Molecular radiotherapy is at the relatively early stage of building-up the evidence for best practice, compared to EBRT trials that have established guidelines. The MRT community needs to build on the EBRT experience and the RTTQA plan to incorporate similar QA processes into MRT dosimetry trials, to ensure accurate and consistent MRT dosimetry between centres.

MOVING FORWARDS

The session started with Dr Samantha Terry, Lecturer in Radiobiology at King's College London and Dr Nadia Falzone, Senior Research Physicist at the University of Oxford, highlighting the importance of radiobiology in MRT. Dr Terry illustrated the use of elegant cell-free DNA assays to evaluate the radiobiology of Auger electron-emitters in her talk entitled *Auger emitters for MRT*. Auger electron-emitters when used as a radiopharmaceutical, could have great potential in the treatment of both cancer and infections. Due to the short

range of the emitted electrons and high ionisation density at the site of decay, Auger electron-emitters are ideal in the treatment of single cells and micrometastases due to their ability to provide precision radiotherapy with little off-target effect. She described the ability of ^{67}Ga to damage DNA and kill cancer cells *in vitro* through both non-targeted and targeted approaches. With the availability of new gallium-chelators providing very high specific activities with facile radiolabelling conditions that could be easily implemented in the clinic, she concluded that ^{67}Ga deserves further investigation as a therapeutic radionuclide in a range of cancers.

Dr Falzone's presentation entitled *Radiobiology for MRT*, highlighted the importance of establishing radiobiological parameters for MRT constructs. Particularly, when using radionuclides that have a significant Auger electron component in their decay scheme and where these constructs internalize and locate to the nucleus of a cell. In this instance, adopting radiobiological sensitivity parameters α and β directly from external beam exposure, may not be accurate. There is a real challenge to evaluate the biological response for MRT constructs. To relate dose to biological effect, quantitative cell culture techniques are used. In itself, this presents a problem as firstly, accurate estimates of dose in the exposed cells are required. As with organ scale dosimetry, the Medical Internal Radiation Dose formalism¹³ can be used to determine dose. However both the decay spectra used for the radionuclide in question and the geometry of the cancer cell can have a huge effect on dose assessment.^{14,15} Furthermore, due to the paucity of α/β ratio data for radionuclides, when relating the dose required to achieve a specific biological effective, α/β ratios for EBRT are used by simply accounting for dose protraction.¹⁶ This presumes that there is no difference in cell killing per unit dose between MRT and EBRT, *i.e.* that the α/β ratios are equivalent. These assumptions need to be confirmed for MRT. Dr Falzone concluded that there is a great need for fundamental research to expound the radiobiology specific to MRT.

The session concluded with Caroline Glover, Research Funding Manager at CRUK detailing different funding streams and funding opportunities within CRUK. She drew attention to the fact that CRUK currently only supports three MRT trials in the Clinical Research Committee Portfolio of which two are focussed on thyroid cancer (IoN—Phase III and SELIMETRY—Phase II) while the other concerns neuroendocrine cancer (LuDo—Phase II). There is great scope for funding MRT trials and she called on the nuclear medicine community to put forward ambitious proposals which bring together the research community around a specific problem and which, if successful, would result in a significant step forward against the CRUK research strategy.

CONCLUSION

In recent years, Molecular Radiotherapy has undergone a renaissance with an unprecedented expansion of radioligands for imaging and therapy. In the UK alone, several clinical trials that incorporate MRT, as highlighted here, are currently underway. This again underscores the importance of appropriate and adequate QA processes and the need to standardise dosimetry. There is also a growing realisation that dosimetry alone is not sufficient to realize

the full potential of MRT but that radiobiologically informed treatment should be incorporated in treatment planning.

The future for MRT is indeed promising. A concerted effort from the multidisciplinary MRT community is now needed

to propose new trials and to undertake preclinical research programmes to ensure the expansion and prosperity of this field.

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